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IN THE EUROPEAN PATENT OFFICE

In re: European Patent No. : 0 011 385 B1

European Appln. No. : 08 111976.3

Applicant/Proprietor : United States of America as represented by the Secretary, United States Department of Commerce

DECLARATION OF DR. DENNIS HRUBY

DENNIS HRUBY DECLARES AND SAYS THAT:

1. I am advised that Virogenetics Corporation lodged an opposition against the above-referenced patent and application, citing inter alia, the Abstracts and information disseminated publicly at the September 20-23, 1982 Poxvirus-Iridovirus Workshop held at Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (the "September 20-23, 1982 Workshop"). I am advised and therefore believe that the Applicant/Proprietor has asserted, inter alia, that the Abstracts presented at the September 20-23, 1982 were confidential and, that the first public dissemination of the contents of the article, "Vaccinia virus: A selectable eukaryotic cloning and expression vector," Proc. Natl. Acad. Sci. USA 79:7415-7419 (December 1982) ("PNAS article") (copy attached), was by the December 8, 1982 publication of the PNAS article (because distribution of the Abstract (copy attached) and presentation of the same title during the September 20-23, 1982 Workshop was not a public disclosure because of some sort of "confidentiality").

2. I was in attendance at and a participant in the September 20-23, 1982 Workshop. Note my name on the Participant-Housing List and Author List and, the Abstract at pages 57, 60 and 61, in which I am an author. I have a copy of the Participant-Housing List, Author List and Abstracts from the September 20-23, 1982 Workshop and understand that a copy is also of record as document D4 in the opposition lodged against the above-referenced patent and application. I have

no interest in the above-referenced patent and application. I also have no interest in the parties to the opposition lodged against the above-referenced patent. Further, I am not a licensee or otherwise presently in or negotiating any business relationship with the parties to the opposition lodged against the above-referenced patent; nor am I a former employee of either of those parties. I am therefore competent to speak without bias about events that occurred at the September 20-23, 1982 Workshop, including the nature of disclosure thereat through presentation of Abstracts and information.

3. I am advised and therefore believe that in support of its assertions, the Applicant/Proprietor relies upon the Agenda for the September 20, 1982 Business and Organizational Meeting of the September 20-23, 1982 Workshop, including, "Should material presented at Pox-Iridovirus Conference be generally referenced in publications?" This reliance is misplaced. The first issue in the Agenda (copy attached) was **not** about whether the "material presented" (Abstracts, presentations and information thereof) was confidential or privileged, but rather that the "material presented" should be referenced as a "personal communication" in publications due to lack of peer review of the material presented. Material presented was nonetheless usable and not confidential or privileged. That is, the first issue of the Agenda only dealt with citation form. I have no recollection of the issue of confidentiality being addressed or any decision of imposing an obligation of confidentiality or privilege on the "material presented", especially since such an obligation would have been wholly contrary to the concept of the Workshop, namely public dissemination.

4. Moreover, I was a presenter, as well as an attendee at the September 20-23, 1982 Workshop. At the time of the September 20-23, 1982 Workshop the Abstracts were assembled (collated) as sequentially numbered pages stapled together. The Abstracts were submitted by presenters prior to the Workshop dates for public dissemination at the Workshop without any promise, express or implied, or other obligation

of confidentiality or of any rights reserved by the presenter. The Abstracts were freely distributed, without any obligation of confidentiality and without any reservation of rights by the presenter, at registration for the Workshop; namely, **before** the first issue of the Agenda was addressed. That is, on the first day of the Workshop (September 20, 1982), before the meeting of that day, and on the day immediately prior thereto (September 19, 1982), the assembled Abstracts were distributed freely at registration for the Workshop, with no obligation of confidentiality or any reservation of rights by the presenter. I mention the day immediately prior to the first day of the Workshop because some participants or attendees of Workshops arrive a day before the first day; for instance, to arrange or settle into lodging during the meeting days. To accommodate early-arriving participants, registration (with distribution freely of the Abstracts, with no obligation of confidentiality or reservation of rights by the presenter), likely occurred on September 19, 1982, the day immediately prior to the first day of the Workshop, and certainly occurred on the first day of the Workshop, before the first meeting. **Thus, the first issue of the Agenda regarding citation form of the September 20, 1982 meeting is irrelevant. The Abstracts had been publicly disseminated prior thereto without any obligation of confidentiality or privilege and without any reservation of rights by any presenter. Accordingly, contrary to the assertions of the Applicant/Proprietor, as of September 19 or 20, 1982, the Abstracts of the September 20-23, 1982 Workshop were publicly disseminated and distributed without any obligation of confidentiality or privilege and without any reservation of rights by the presenter; and the Abstracts were therefore published.**

5. Furthermore, attached is a copy of my Curriculum vitae. I have had a great deal of experience constructing vaccinia virus recombinants for use as expression vectors. I have read and am familiar with the PNAS article and "Construction of Poxviruses as Cloning Vectors: Insertion

of the Thymidine Kinase Gene from Herpes Simples Virus into the DNA of Infectious Vaccinia Virus", *Proc. Natl. Acad. Sci. USA*, Vol. 79, pages 4927-4931, by Panicali (and Paoletti, "the Panicali et al. article"; copy attached). While constructing vaccinia virus recombinants is not a trivial experience, it was with the publication of the Panicali et al. article that enabled recombinant vaccinia virus construction and expression thereby. The PNAS article (i.e., the December 1982 article "Vaccinia Virus: A selectable eukaryotic cloning and expression vector," PNAS USA 79:7415-7419) and likewise the above-captioned patent and application, in my opinion, added little new to the state of the art (and, as discussed below, I am well-qualified to have such an opinion).

6. I have also been provided and have reviewed the papers of record in the opposition, particularly the November 18, 1993 Notice of Opposition and documents D1 to D10 and the August 12, 1994 submission by Proprietor/Applicant and documents D11 to D28, as well as the claims of the above-referenced patent. I am the "D.E. Hruby" cited in D2, Weir et al. PNAS USA 79:1210-1214 (1210, col. 2, lines 30-34), February 1982 ("Weir et al. D2"), which I have read and understood.

7. I am also an author of Hruby and Ball, "Mapping and Identification of the vaccinia virus Thymidine Kinase Gene," J. Virol., 1982, 43:403-409 and Hruby et al., J. Virol. 1981, 40: 456-64 (copy of each attached; respectively "Hruby 1982" and "Hruby 1981"). Thus, in the relevant art, at the relevant time, I was skilled. I am advised and therefore believe that the Panicali et al. article may be read alone or with other documents to ascertain the novelty and inventiveness (obviousness) of the subject matter of the claims of the above-referenced patent. I am also advised and therefore believe that document D9, U.S. Patent No. 4,769,330 ("the '330 Patent"), which I have read and understood, may be relied upon for the content of its specification to anticipate the claims in issue in the opposition.

8. I am further advised that the Applicant/Proprietor asserts patentability and attempts to distinguish from Panicali et al. as follows (original emphasis omitted):

> Because expression in the Panicali and Paoletti constructs was driven by a fortuitously-proximal vaccinia promoter, there can be no assurance that a vaccinia promoter will be sufficiently proximal and in the proper orientation in relation to an insertion site in *another* insertion site or non-essential region. Moreover, there could be no assurance that other poxviruses would have a transcriptional regulatory sequence sufficiently proximal to the insertion sites in the non-essential regions to drive expression.
>
> In view of the limitations of the prior art, the problems confronted by inventors Moss, Mackett and Smith was to provide recombinant poxviruses that could reliably and efficiently express foreign genes with proper fidelity. See, for example, pages 4-5 of Application No. 83111976.3 (on which the Patent in suit is based). The inventive solution was to deliberately employ poxvirus transcriptional regulatory sequences to control the expression of the foreign gene in the recombinant poxvirus. To insure that the poxvirus transcriptional regulatory sequence was free to control expression, no non-poxvirus transcriptional regulatory sequences were placed between the foreign gene and the poxvirus transcriptional regulatory sequence. In accordance with a preferred manner of making such a recombinant virus, the poxvirus regulatory sequence was inserted into the poxvirus along with the foreign gene, which insures that the foreign gene and the poxvirus transcriptional regulatory sequence are in the proper orientation relative to one another. By employing this inventive approach, the inventors did not have to rely upon the fortuitous presence of an endogenous promoters near their insertion site.

9. As shown by the foregoing, I am not only one skilled in the relevant art pertaining to the above-referenced patent and application, I was also such at the relevant time,

as acknowledged in the literature at that time (see Weir et al., D2, at 1210, *loc. cit.*), and, I am therefore competent to address and render expert opinions regarding the assertions of the Applicant/Proprietor, without bias.

10. I respectfully submit that the assertions of the Applicant/Proprietor are incorrect. They are, in my view, based upon narrow, misreadings of the prior art, particularly of documents other than the Abstracts and presentations of the September 20-23, 1982 Workshop. The supposed "limitations" and "solution" asserted by Applicant/Proprietor, in my expert opinion, were anticipated by the '330 Patent and were certainly anticipated or suggested by the Panicali et al. article either alone or in combination with other documents. Such other documents include, Weir et al., D2 (February 1982), and/or Hruby 1982, (August 1982), and/or Venkatesan et al., Cell 125:805-813, September 1981 (D1, which I have read and understood), together with Molecular Biology of the Gene, p. 714 (3d Ed. by James Watson, 1976) (a standard textbook), and Pribnow, "Genetic Control Signals in DNA", ch. 7 in Volume 1, "Gene Expression" of Biological Regulation and Development (edited by Robert F. Goldbeyer) ("Pribnow"), 1980, especially Sections 2.1, "The Transcript Unit", and 3.1, "The Promoter," p. 230, 231, alone or with at least one of Rosenberg and Court (1979), "Regulatory sequences involved in the promotion and termination of RNA transcription," Ann. Rev. Genetics 13:319-353 and Breathnach and Chambon (1981), "Organization and expression of eucaryotic split genes coding for proteins," Ann. Rev. Biochem. 50:349-383. For convenient reference, a copy of each of Molecular Biology of the Gene, p. 714, Pribnow, Rosenberg and Court, and Breathnach and Chambon, which I have read and understood, is attached. Also, in this regard, mention is made of Moss et al., "Deletion of a 9,000-Base-Pair Segment of the Vaccinia Virus Genome that Encodes Nonessential Polypeptides," J. Virol., 1981, 40: 387-95 (D21, which I have read and understood), Panicali et al., "Two Major DNA Variants ...", J. Virol., 1981, 37:1000-1010 (which I have read and understood and, a copy of which is attached;

"Panicali et al. 1981") and Hruby 1981, which can be read with the Panicali et al. article alone or collectively and/or with any of the other documents above-cited.

11. Considering first the Panicali et al. article and the '330 Patent, the assertions by the Applicant/Proprietor that the Panicali et al. article and the '330 Patent "disclose[] that the inserted HSV TK gene must contain its own herpes promoter in order to obtain transcriptional expression" and that it is somehow novel or nonobvious to "employ poxvirus transcriptional regulatory sequences to control ... expression" are incorrect.

12. The Panicali et al. article and the '330 Patent disclose the construction of six vaccinia virus HSV TK recombinants and the expression by three of those recombinants. More specifically, the Panicali et al. article and the '330 Patent disclose VP1 to VP6. VP1, VP3 and VP5 were derived from pDP132 and VP2, VP4 and VP6 were derived from pDP137. The direction of the Bam HSV TK fragment in each of pDP132 and pDP137 were opposite to the other, to thereby obtain expression regardless of whether expression is under the control of HSV DNA acting as a promoter or a vaccinia promoter and, to ascertain logically which of these indeed controlled expression.

13. VP2, VP4 and VP6 all expressed the HSV TK gene, whereas VP1, VP3 and VP5 did not, because of the orientation of the gene in these recombinants. **The Panicali et al. article at page 4931 clearly states: "That vaccinia signals may be operative for HSV TK expression" in VP2, VP4 and VP6. That is, of the two possibilities, i.e., of whether certain HSV DNA acted as a promoter or whether a vaccinia promoter controlled expression, the Panicali et al. article clearly teaches and suggests that it is the vaccinia signals which are operative.**

14. Moreover, in view of expression by VP2, VP4 and VP6 and not by VP1, VP3 and VP5, the '330 Patent discloses that "**the HSV TK-modified F-fragment is incorporated into the vaccinia variants** in the cell **and is then capable of**

replication and **expression under vaccinia control**" (col. 10, lines 7 to 10; emphasis added). This text also appears in D7, EP-A2083 286, which claims priority from U.S. application Serial No. 334,456, filed December 24, 1981 from which the '330 Patent issued. This is clearly a teaching that expression of the foreign gene in the recombinant vaccinia virus (VP2, VP4 and VP6) was by vaccinia (poxvirus) regulatory sequences (control). Also, the '330 Patent in the text at column 2, line 63 to column 3, line 1, teaches "incorporation, into the mutant [i.e., in the exogenous DNA], of tandem repeats of the gene ... or of additional genetic elements ... or ... the use of a strong promoter"; that is, the '330 Patent clearly teaches that the exogenous DNA can contain several genetic elements, including "a strong promoter". This text also appears in D7. Thus, the '330 Patent clearly teaches a recombinant vaccinia virus wherein there is expression under vaccinia control (promoter) and, wherein the exogenous DNA can contain several genetic elements, including "a strong promoter."

15. There is simply nothing novel or nonobvious in the claims of the above-referenced patent and application (which I have read and understood and, a copy of which are attached), in view of the Panicali et al. article teachings and suggestions and the '330 Patent expressly teaching that expression in vaccinia virus recombinants of the exogenous DNA is under vaccinia control (promoter) and not by virtue of exogenous HSV DNA acting as a promoter, and by expressly teaching that the exogenous DNA can contain several genetic elements, including "a strong promoter" (which would be a vaccinia promoter since expression is taught as under vaccinia control).

16. This conclusion is furthered by considering the state of the art, particularly as shown by the documents cited herein which are of record or attached. In this regard, it is noted that even if the very clear teachings and suggestions and teachings, respectively, of the Panicali et al. article and of the '330 Patent quoted above, were not in the text of

the Panicali et al. article or the '330 Patent, the probability of that which controlled expression in the constructs VP2, VP4 and VP6 facing the skilled artisan was a mere coin toss, a 50-50 chance: either exogenous HSV DNA acted as a promoter; or expression of the exogenous DNA was under vaccinia control (promoter); i.e., expression was from only one of two possibilities.

17. I note the disclosure of Panicali et al. 1981 in view of the disclosure of Moss et al. in D21, wherein Moss et al. confirm the observations of Panicali et al. 1981 and, which at 394 states:

> The deletion described here appears to be very similar to the one recently reported by Panicali et al. (17) in a stable "small DNA" variant. Indeed, we suspect that it is identical since their serially passaged stock was obtained originally from our laboratory.
>
> The deletion within the vaccinia virus genome had no apparent effect on specific infectivity or virus yield in HeLa cells or plaque size in BSC-1 cells (14). Our preliminary experiments also indicated that variant 6/1 and 6/2 replicated in pig kidney cells (kindly supplied by R. Moyer) in contrast to the host range effects seen with some rabbitpox deletion mutants (16). Therefore, it was of particular interest to determine whether the deletion was in a silent or expressed region of the vaccinia virus genome. Blot hybridization studies of Panicali et al. (17) suggested that the region is an immediate early or early transcriptional unit. Recent translational and transcriptional maps of the left side of the genome reproduced in Fig. 5 indicated that the deleted region encodes a minimum of seven or eight immediate early as well as two minor late polypeptides (4, 25). In this report, the absence of all of these early mRNA's in cells infected with the deletion mutant was established by cell-free translation experiments.

It was certainly not merely fortuitous that a vaccinia promoter was proximal in VP2, VP4 and VP6. Rather, by

reviewing orientation of VP1 to VP6 and expression by VP2, VP4 and VP6, it is clear that as stated in the '330 Patent and as taught and suggested in the Panicali et al. article, expression was under vaccinia control. It was not merely fortuitous that expression was by a proximal vaccinia promoter in the Paoletti et al. article or the '330 Patent. As shown by Moss et al. 1981 (D21) and Paoletti et al. 1981, the vaccinia genome was known to contain numerous promoters. Note, for instance, that in one region of the vaccinia genome Moss et al. 1981 (D21) confirmed that it was "an immediate early or early transcriptional unit [which] ... encodes a minimum of seven or eight immediate early ... polypeptides." Note again '330 Patent teaching that the exogenous DNA can contain several genetic elements, including "a strong promoter" (which must be a vaccinia promoter, since the '330 Patent teaches expression under vaccinia control).

18. Note too that as shown in Pribnow, Section 2.1 at p.230 a "transcriptional unit is a stretch of DNA base pairs bounded on one end by a 'start sequence' or *promoter* ... and the other end by a 'stop sequence' or *terminator* "(emphasis in original). Note further that while Applicant/Proprietor admits,

> D1 [Venkatesan et al., Cell 125 805-813 September 1981] discusses the 5' region containing RNA start site of the vaccinia gene encoding a 7.5 Kd polypeptide ... Sequences corresponding to this region were later used to obtain the vaccinia 7.5 K promoter,

it is important to point out that the "5' region containing the RNA start site of the vaccinia gene encoding a 7.5 Kd polypeptide" <u>is</u> "the vaccinia 7.5 K promoter". Thus, the sequence of the 7.5 K promoter <u>was</u> disclosed in D1. No further information other than the information disclosed in D1 was required to "obtain the vaccinia 7.5 K promoter". Accordingly, the Panicali et al. article or the '330 Patent, either alone or in view of D1, anticipated or rendered obvious the claims of the above-referenced patent and application,

especially in view of the following detailed discussion of the state of the art.

19. A standard textbook published in 1976 defines a promoter as a "[r]egion on DNA at which RNA polymerase binds and initiates transcription" (p. 714, Molecular Biology of the Gene, 3rd edition, by James Watson). Similarly, in 1980 David Pribnow stated "The basic promoter is only that particular DNA sequence that is recognized directly and used by the RNA polymerase as a start signal for transcription" (Pribnow 1980, section 3.1 "The Promoter", p. 231).

20. The nature of and elements contained within both procaryotic and eucaryotic promoters were well defined before the priority date of the above-captioned patent and application, which I am advised and therefore believe was November 30, 1982. (Rosenberg and Court, 1979; Pribnow 1980; Breathnach and Chambron, 1981). In particular, it was well established that promoters are commonly located upstream from the ATG initiation of translation sites which begin DNA sequences coding for proteins. In D1, the authors demonstrate extensive familiarity with this knowledge in the state of the art by citing and discussing several publications which reveal elements and characteristics of various procaryotic and eucaryotic promoters (Rosenberg and Court, 1979; Pribnow 1980; Benoist et al., 1980; Flavell et al., 1979; Canaani et al., 1979; Baker et al., 1979; Hashimoto and Green, 1980). The authors of D1 also discuss the occurrence of sequence motifs near the potential AUG initiation of translation sites in the 7.5K mRNA which are similar to sequence motifs found near the initiation of translation codons found in various other virus RNAs (vesicular stomatitis virus RNA, alfalfa mosaic virus RNA 4: Rose 1978; late adenovirus mRNA: Ziff and Evans, 1978; turnip yellow mosaic virus mRNA: Briand et al., 1978).

21. In its title (p. 805) D1 disclosed, "distinctive nucleotide sequence adjacent to multiple initiation ... sites of an early vaccinia virus gene" (i.e., the 7.5 Kd gene; emphasis added).

22. The summary of D1 (p. 805) includes the following:

> A remarkable 88% AT-rich 60 bp DNA sequence was found immediately upstream of the initiation of transcription sites. Although DNA sequences that bear some homology to Pribnow and Hogness boxes are present, additional recognition sequences located further upstream of procaryotic and eucaryotic initiation sites are absent. A possible initiation of translation codon occurs about 50 nucelotides from the 5′ end of the message.

23. The preceding quote (in paragraph 22) clearly describes sequence characteristics of the 7.5 promoter, in comparison to the sequences of canonical procaryotic promoters (which contain a Pribnow box) and eucaryotic promoters (which contain a Hogness box). As the authors in D1 note (p. 810).

> AT-rich sequences previously have been found within the promoter regions of procaryotic and eucaryotic mRNAs AT-rich region near the viral initiation of transcription site showed some homology to similar regions of procaryotic and eucaryotic genomes, additional homology was not found further upstream.

24. In D1 the authors further note (p. 805), col. 1. lines 7-14) that

> Recently several mRNAs made early after vaccinia virus infection ... and in vitro by virus cores (Venkatesan and Moss, 1981) have been mapped on the vaccinia virus genome. These early mRNAs are not spliced and their cap structures retain the β-^{32}P-label of the initiating nucleotide, indicating the absence of processing at the 5′-end.

25. As the authors of D1 stress (p. 809), referring to the mRNA for the 7.5 polypeptide,

> the β-phosphate of GTP previously was shown to be incorporated into cap structures of this mRNA, providing evidence of the strongest kind that the 5′ ends represent true initiation sites (Venkatesan and Moss, 1981)

(i.e., that the 5′ end of the mRNA maps to the 7.5 K promoter region).

26. Finally, (at p.811) the authors of D1 conclude

> The multisubunit RNA polymerase of vaccinia virus, like that of procaryotic and eucaryotic organisms, must be capable of interacting with the promoter sequences for a large number of RNAs. Efforts to extend the present studies by sequencing additional genes are in progress.

27. It is thus evident that the DNA sequences disclosed in D1 around the 5' end of the mRNA for the 7.5 polypeptide are in fact and were at the time of publication thereof known to be the promoter sequences for the 7.5 K gene. Thus, the Panicali et al. article taken alone or with D1, and alternatively in further combination with Panicali et al. 1981 or Moss et al. 1981 (D21) or with both of Panicali et al. 1981 and Moss et al. 1981 (D21) placed into the skilled artisan's hands:

- recombinant vaccinia virus;
- with the expression of exogenous DNA therein under vaccinia control;
- with the exogenous DNA therein deliberately placed proximinal to vaccinia promoters;
- the 7.5 K promoter; and,
- that the 7.5 K promoter naturally occurs adjacent to the coding sequence for the 7.5 K polypeptide.

28. Accordingly, without inventive effort, one skilled in the art could place desired exogenous DNA proximinal to a vaccinia promoter and, could place a desired promoter such as the 7.5 K promoter adjacent to coding DNA, as such occurs naturally with respect to the 7.5 K promoter and coding sequence for the 7.5 K polypeptide, as shown by D1, when read in the light of the knowledge in the art and the documents D1 itself cites.

29. With respect to Weir et al. D2, since this article discloses that "the vaccinia thymidine kinase gene maps to the 5,000 bp *Hin*dIII J fragment", the "person of skill in the art", who wished to obtain a vaccinia TK promoter would naturally focus his search to sequences within the vaccinia *Hin*dIII J fragment. The "person of skill in the art" would

expect that the TK promoter would be located in "upstream sequences of the TK gene". In D2, the authors acknowledge that they are not the only group that had mapped the TK gene to *Hind*III J (D2, p. 1210, col. 2, lines 30-34): "Further evidence that the *Hind*III J fragment contains the structural TK gene was obtained in our laboratory and in that of D.E. Hruby and L.A. Ball (personal communication) by cell-free translation of hybridization selected mRNA under conditions suitable for expression of active TK."

30. Prior to November 30, 1982, Dr. Ball and I, in Hruby 1982, reported in detail the location of the vaccinia TK gene. In Hruby 1982, Dr. Ball and I were the first to report that the vaccinia TK gene was transcribed as a 700 nt RNA, and that, contrary to previous expectations, the gene encoded a 19 kilodalton protein. We also reported that "the tk gene lies completely within *Hind*III fragment J, and this conclusion is supported by recent analyses of subfragments of J, which show that the gene lies between about 0.5 and 1.2 kilosbases from the L-J boundary". We also disclosed that "the structural gene for VVtk is located in *Hind*III fragment J at 42.5 to 45.1 map units". Thus, prior to the above-captioned patent and application, information was available in the public domain which could be used by persons "of skill in the art" to obtain the vaccinia TK promoter, without any inventive efforts. Note also Hruby 1981.

31. Further, the Panicali et al. article with Hruby 1982, either alone or in combination with any one or all of D1, Weir et al., D2, Panicali et al. 1981, Moss et al. 1981 (D21) and any other document cited herein of record or attached, placed into the knowledge of the skilled artisan:

- recombinant vaccinia virus;
- with expression of exogenous DNA therein under vaccinia control;
- with exogenous DNA therein deliberately placed proximal to vaccinia promoters;
- the 7.5 K promoter;

- that the 7.5 K promoter naturally occurs adjacent to the coding sequence for the 7.5 K polypeptide; and,

- the mapping and identification of the vaccinia virus thymidine kinase gene.

32. Accordingly, without inventive effort, one skilled in the art: could place desired exogenous DNA proximal to a vaccinia promoter; could place a desired promoter, such as the 7.5 K promoter, adjacent to coding DNA, as such occurs naturally with respect to the 7.5 K promoter and coding sequence for the 7.5 K polypeptide; and, could locate the vaccinia virus TK promoter by looking to sequences upstream from the mapped and identified gene therefor, since promoters for other vaccinia virus genes, such as for the 7.5 K polypeptide, were known to be adjacent to and upstream from the gene.

33. From the literature, it is clear that "deliberately employ[ing] poxvirus transcriptional regulatory sequences to control expression of the foreign gene" such as by inserting "the poxvirus regulatory sequence ... into the poxvirus along with the foreign gene" was within the ambit of the skilled artisan and, was a simple duplication of that which had already been disclosed, particularly as naturally occurring with respect to the 7.5 K polypeptide gene and the promoter therefor. The exogenous DNA in the Panicali et al. article and the '330 patent was expressed under vaccinia control and was <u>not</u> "fortuitously-proximal [to a] vaccinia virus promoter" as asserted by the Applicant/Proprietor.

34. Thus, not only do I heartily disagree with the Applicant/Proprietor's recent recreation of the history of the September 20-23, 1982 Workshop, I also strongly disagree with the Applicant/Proprietor's assertions of alleged invention and of the state of the art. The state of the art was far more advanced than asserted by the Applicant/Proprietor and, in view of the state of the art, the Applicant/Proprietor's alleged invention is merely a disclosed or obvious variant of the state of the art and, by no means any invention.

35. The claims of the above-referenced patent and application are not novel or nonobvious in view of the Panicali et al. article or the '330 patent, either alone or in view of other art such as documents cited herein and attached or which are already of record.

I further declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true.

Date: 3-6-95

Dennis E Hruby

Dr. Dennis Hruby